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Radical-based methodology for efficient generation of acyclic *N*-acylimines

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Abstract

α-Methoxybenzamides **11**, which are convenient precursors of acyclic *N*-acylimines, can be cleanly generated in high yields via a free radical process starting from an *o*-aminobenzamide **16** derived from an *N*-*t*-butyl or *N*-cumyl secondary amine.

Keywords: radicals and radical reactions; amides; nitrogen heterocycles; allylation; Diels–Alder reactions.

We have recently reported a new strategy for preparation of α-methoxybenzamides, which are very useful *N*-acyliminium ion precursors,[1,2] based upon some observations made many years ago by Turpin and Hey,[3] and followed up by Cohen and coworkers[4,5] in some insightful mechanistic investigations. As shown in Scheme 1, we developed a simple one-pot method to convert *o*-aminobenzamides **1**, which are very easily prepared by the reaction of amines with isatoic anhydride,[6] to α-methoxybenzamides **6**. The overall process involves as key steps an in situ diazotization of **1** to give **2**, [1,5]-hydrogen atom translocation in aryl radical **3**, followed by oxidation of the new radical **4** by Cu^{+2} to the *N*-acyliminium species **5**. Subsequent in situ trapping of unstable intermediate **5** by solvent gives the α-methoxybenzamide **6**. We have also spent considerable time investigating the regioselectivity of this procedure in cases involving unsymmetrical *o*-aminobenzamides of cyclic secondary amines.[2] To briefly summarize these results, oxidations of unsymmetrical *o*-aminobenzamide derivatives of pyrrolidines and piperidines generally show good regioselectivity for methylene over methine oxidation, particularly when the α-substituent R in **1** is large. We have rationalized the observed regioselectivity of this process based upon a hypothesis involving amide rotamer populations of the intermediate aryl radical (cf. **3**).[2,5]

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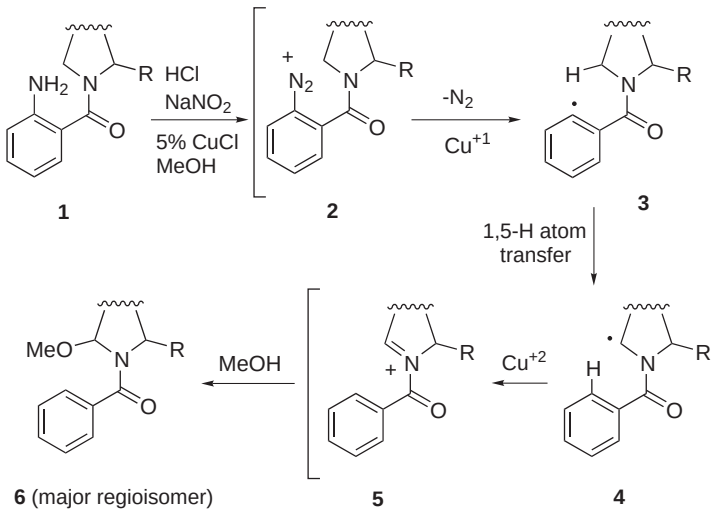
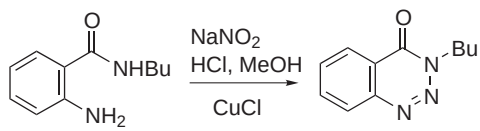


Scheme 1.

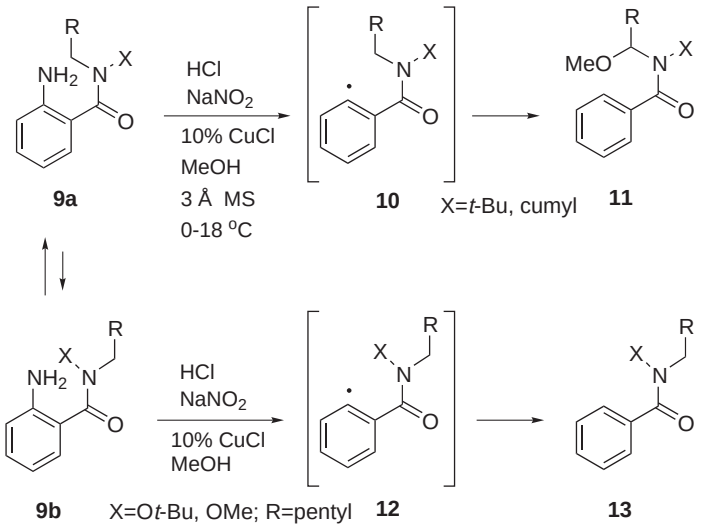
One limitation of the methodology is that an *o*-aminobenzamide **7** of a primary amine does not undergo the desired radical oxidation process upon diazotization in the presence of CuCl, but rather forms a stable triazine **8** (Eq. (1)). In order to solve this problem, and to extend the scope and utility of this chemistry, we have begun to investigate acyclic systems of type **9a**/**b** (Scheme 2). The strategy here is to have group 'X' on nitrogen be easily removable, thereby making these systems equivalent to effecting the oxidation chemistry with a primary amine derivative. Moreover, since the hypothesis is that amide rotamer populations control the regioselectivity of the process, we expected that having a large, bulky 'X' group would bias the system towards rotamer **9a**, a critical feature which should lead to efficient oxidation to ultimately afford the desired α-methoxybenzamides **11**, precursors to acyclic *N*-acylimines. It should be noted that little good methodology is available for preparation of *N*-acylimines derived from simple aldehydes, and even fewer methods are known which produce such species from ketones.[7]



(1)

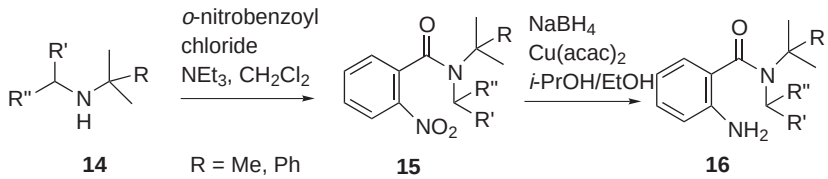
Some initial feasibility experiments were conducted with the *O*-alkyl hydroxamic acid derivatives **9a**/**b** (X = O*t*-Bu and OMe, R = pentyl), which upon exposure to our standard diazotization/oxidation conditions[2] afforded complex mixtures containing low to moderate yields of reduction products **13** as the only identifiable compounds (Scheme 2). It is probable that **13** arises via hydrogen atom abstraction from solvent by intermediate aryl radical rotamer **12**, which is incapable of a 1,5-hydrogen atom migration. We were pleased to find, however, that if the 'X' substituent on nitrogen is changed to *t*-butyl or cumyl,[8] oxidation in fact leads to the desired α-methoxybenzamides **11** in excellent yields, presumably via amide rotamer **10**. In this communication we describe the development of this chemistry into a practical synthetic method.

The substrates for these studies were prepared starting from the appropriate *t*-butyl or cumyl amine derivative **14**,[8,9] which was first acylated with *o*-nitrobenzoyl chloride to afford amides **15**



Scheme 2.

(Scheme 3). In these systems, the rather bulky acyclic amines did not acylate well with isatoic anhydride.[6] Reduction of the nitro group then afforded the *o*-aminobenzamide substrates **16** in good overall yields. We have developed a standard set of oxidation conditions[10] which have been tested with a number of these *o*-aminobenzamides **16** to generate α-methoxybenzamides like **11** (cf. Scheme 2), and the results are listed in Table 1. As can be seen, product yields are high in all the cases involving oxidation at a methylene carbon. However, the methine system shown in entry 9 led to the corresponding enamide rather than the methoxy compound, but only in moderate yield. It is not clear what the problem is in this case, but since as noted above *N*-acylimines derived from simple ketones are not readily available,[1] we intend to investigate such systems further.

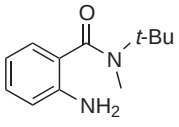
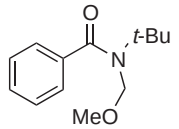
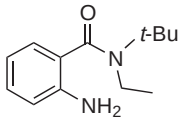
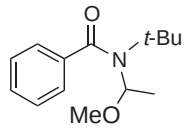
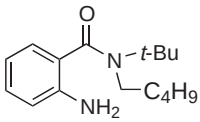
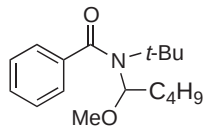
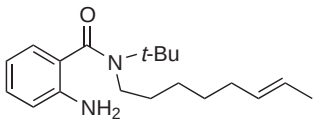
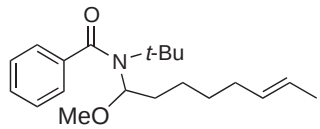
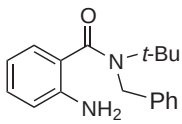
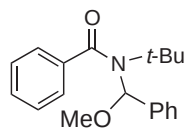
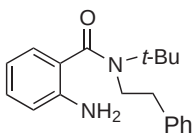
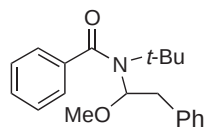
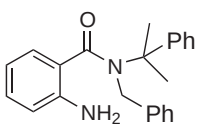
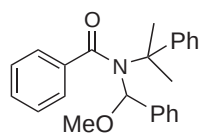
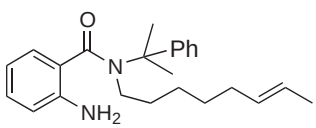
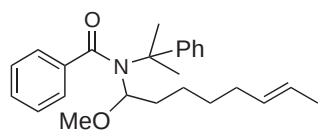
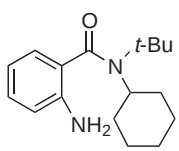
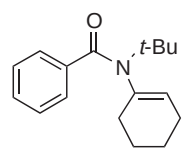


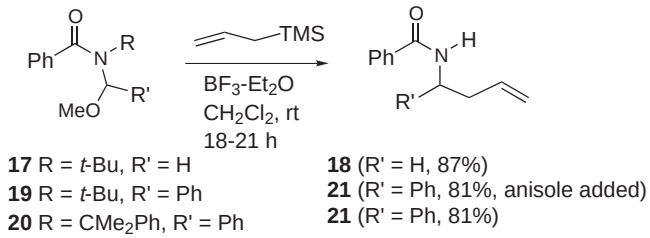
Scheme 3.

We have also tried a few reactions of the *N*-acylimines generated from some of the oxidation products in Table 1. Thus, α-methoxybenzamide **17** reacts with allyltrimethylsilane at room temperature in the presence of boron trifluoride etherate to afford allylation product **18** with concomitant cleavage of the *N*-*t*-butyl group (Scheme 4). Similarly, allylation of substrate **19** (anisole used as a cation scavenger) and the corresponding *N*-cumyl system **20** led to the *N*-dealkylated product **21** in good yields.

In addition, α-methoxybenzamides **22a** and **22b** are good substrates for hetero Diels–Alder cycloadditions.[11] Treatment of **22a** with boron trifluoride etherate/methanesulfonic acid overnight leads to a stereospecific [4+2]-cyclization[11] via the corresponding *N*-acyliminium intermediate **23** to afford bicyclic oxazine **24**, which is identical to the compound which we have

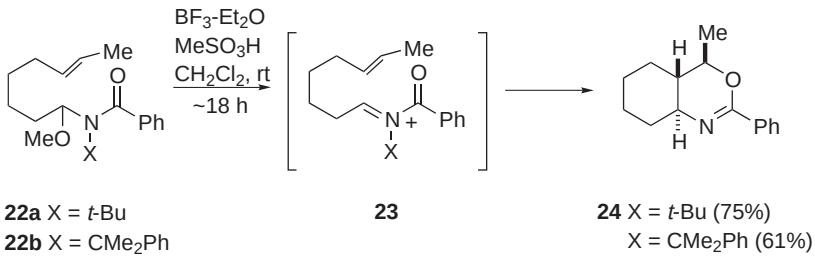
Table 1
Conversion of *N*-alkyl-*o*-aminobenzamides to α-methoxybenzamides[9]

entry	*o*-aminobenzamide	reaction time	product	yield (%)
1		1.5 h		93
2		1.5 h		94
3		2.0 h		82
4		1.5 h		91
5		3.5 h		99
6		3.0 h		94
7		3.0 h		92
8		3.5 h		92
9		3.0 h		47



Scheme 4.

previously prepared[11] (Scheme 5). It is not clear here whether cleavage of the *N*-*t*-butyl group precedes the cycloaddition (i.e. X = BF_3 or H in imine **23**) or occurs afterwards. The *N*-cumyl system **22b** also successfully cyclizes to the same product **24**.



Scheme 5.

In summary, we have developed a simple, high yielding new route to produce α-methoxybenzamides, which are stable, storable precursors to *N*-acylimines formally derived from simple aldehydes and ketones. We are currently investigating extensions and applications of this methodology to alkaloid total synthesis.

Acknowledgements

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5. See also: (a) Snieckus, V.; Cuevas, J.-C.; Sloan, C. P.; Liu, H.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 896. (b) Curran, D. P.; Liu, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1377 and references cited therein. Interestingly, the translocated radicals in our system (cf. **4**) do not cylize back onto the aromatic ring as observed by Curran, presumably because Cu-promoted oxidation to the *N*-acylimine is faster.
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9. The secondary *t*-butyl amines used to prepare the substrates in entries 1 and 5 of Table 1 are commercially available. Others were prepared by routine chemistry.
10. Experimental procedure for oxidation of *o*-aminobenzamides **16**: The *o*-aminobenzamide (1.0 equiv.) and $NaNO_2$ (1.5 equiv.) were dissolved in dry methanol (0.07 M solution) in a clean two-necked flask (free of contamination with copper). To this solution at 0°C was added dropwise 1.0 M methanolic HCl (5.6 equiv.) over 10 min and the mixture was stirred at this temperature for an additional 50 min until the starting material was converted to the diazonium salt (determined by TLC). Powdered molecular sieves (3 Å, loaded in a flask connected by a ground glass joint, predried over a flame in vacuo for 20 min) were quickly added and the mixture was stirred for 10 min. Anhydrous cuprous chloride (0.1 equiv.) was then added and the mixture was stirred at 12–18°C for 1.5 h. The mixture was filtered through Celite and the pad was rinsed with methanol. The filtrate was neutralized with NaOMe (7.0 equiv.) and the methanol was removed under reduced pressure. The residue was purified by flash chromatography on activated neutral alumina (to which 5% water was added) eluting with 14:1 hexanes/ethyl acetate to afford the α-methoxybenzamide.
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